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Liver Neurobiology: Regulation of Liver Functions by the Nervous System

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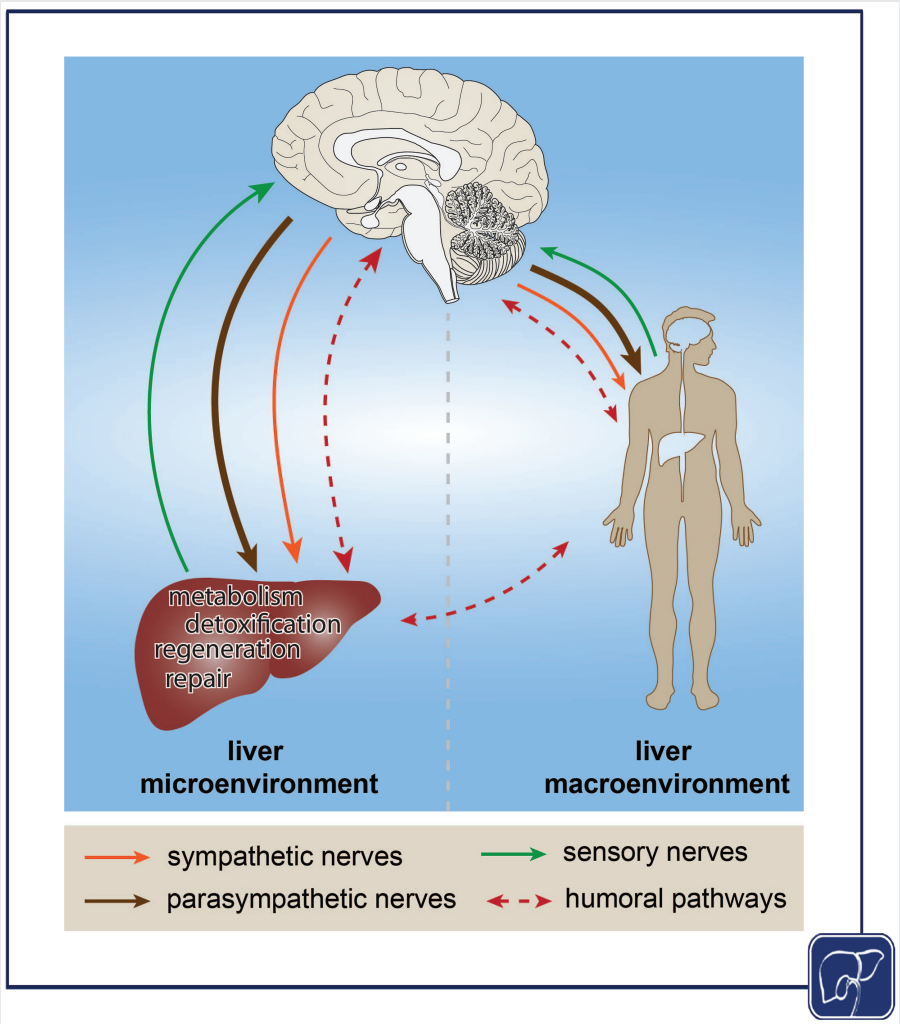
Graphical Abstract



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Abstract

The nervous system plays an important role in the regulation of liver functions during physiological as well as pathological conditions. This regulatory effect is based on the processing of signals transmitted to the brain by sensory nerves innervating the liver tissue and other visceral organs and by humoral pathways transmitting signals from peripheral tissues and organs. Based on these signals, the brain modulates metabolism, detoxification, regeneration, repair, inflammation, and other processes occurring in the liver. The nervous system thus determines the functional and morphological characteristics of the liver. Liver innervation also mediates the influence of psychosocial factors on liver functions. The aim of this review is to describe complexity of bidirectional interactions between the brain and liver and to characterize the mechanisms and pathways through which the nervous system influences liver function during physiological conditions and maintains liver and systemic homeostasis.

Keywords

- cholinergic anti-inflammatory pathway
- sympathetic nervous system
- sensory nerves
- stress
- vagus nerve

Lay Summary

The brain–liver axis plays an important role in the regulation of liver functions, regeneration, repair, and inflammation. The principal components of the brain–liver axis include sympathetic, parasympathetic, and sensory nerves as well as humoral pathways. The nervous system influences liver function also indirectly through the neuroendocrine–immune network that allows the brain modulate processes in both the liver micro- and macroenvironment.

The nervous system plays an important role in the regulation of the activity of visceral organs, including the largest of them, the liver.[1] The brain maintains cellular and tissue homeostasis in liver directly as well as through the neuroendocrine–immune network (►**Fig. 1**). This homeostatic control also includes the adaptive and compensatory responses of the nervous system to liver damage and to processes associated with liver regeneration, repair, and inflammation.[2] In these homeostatic regulations, signals transmitted from the liver by afferent nerves and humoral pathways play an important role, as well.[3] Research on bidirectional interactions between the brain and the liver during physiological and pathological conditions falls within the field of liver neurobiology.

The aim of this review is to provide an overview of current knowledge regarding the brain–liver interactions during physiological conditions. First, the concept of the brain–liver axis is described, as it was originally focused on the influence of the liver on brain function. Then, the new concept of bidirectional brain–liver interactions is characterized, which is based on the transmission of signals directly through afferent and efferent nerves connecting the brain and liver, as well as indirect transmission involving a neuroendocrine–immune network that interacts in a complex manner with the liver. The role of the brain–liver axis in the regulation of homeostasis is described next, both in view of the metabolic functions of the liver and in view of the inflammatory and reparative processes occurring in the liver. Brain structures involved in the processing of afferent signals transmitted from the liver and efferent signals regulating liver function are also discussed. The last section discusses psychoneuroimmunology and the impact of stress on the development and progression of liver disease and includes a section describing our own observations.

Although that is not the aim of this review, it should be noted that the brain–liver axis plays an important role not only during physiological but also during pathological conditions. It is well documented by findings showing that the nervous system influences the onset and progression of pathological processes affecting liver (for more details see[2,4,5]).

Brain–Liver Axis

In the past, the term brain–liver axis was used mainly in studies investigating the mechanisms by which impaired liver function in cirrhotic patients, leading to hyperammonia and elevated concentrations of other toxic substances, contributed to hepatic encephalopathy (HE) or dementia.[6,7] Recently, it was suggested that in effect of hyperammonia on brain activity, nerve pathways are involved. Specifically, signals transmitted by afferent pathways of the vagus nerve from the liver to the brain as well as signals transmitted by efferent pathways of the vagus nerve from the brain to the gut are related to the development of HE (►**Fig. 2**).[6]

However, in the context of neurobiological research on liver, the term the brain–liver axis used in this review refers to bidirectional interactions between the liver and the brain, mediated mainly by autonomic and sensory nerves (►**Fig. 3**) but also by humoral pathways. Besides these direct interactions, brain–liver axis may act on liver also indirectly, by involving the endocrine and immune system or other cells, tissues, and organs (►**Fig. 1**). An example of indirect interactions is the transmission of signals from the digestive tract, skeletal muscle, and adipose tissue to the brain, which increases the efficiency of the regulation of metabolic processes in the body.[8,9] The brain also regulates

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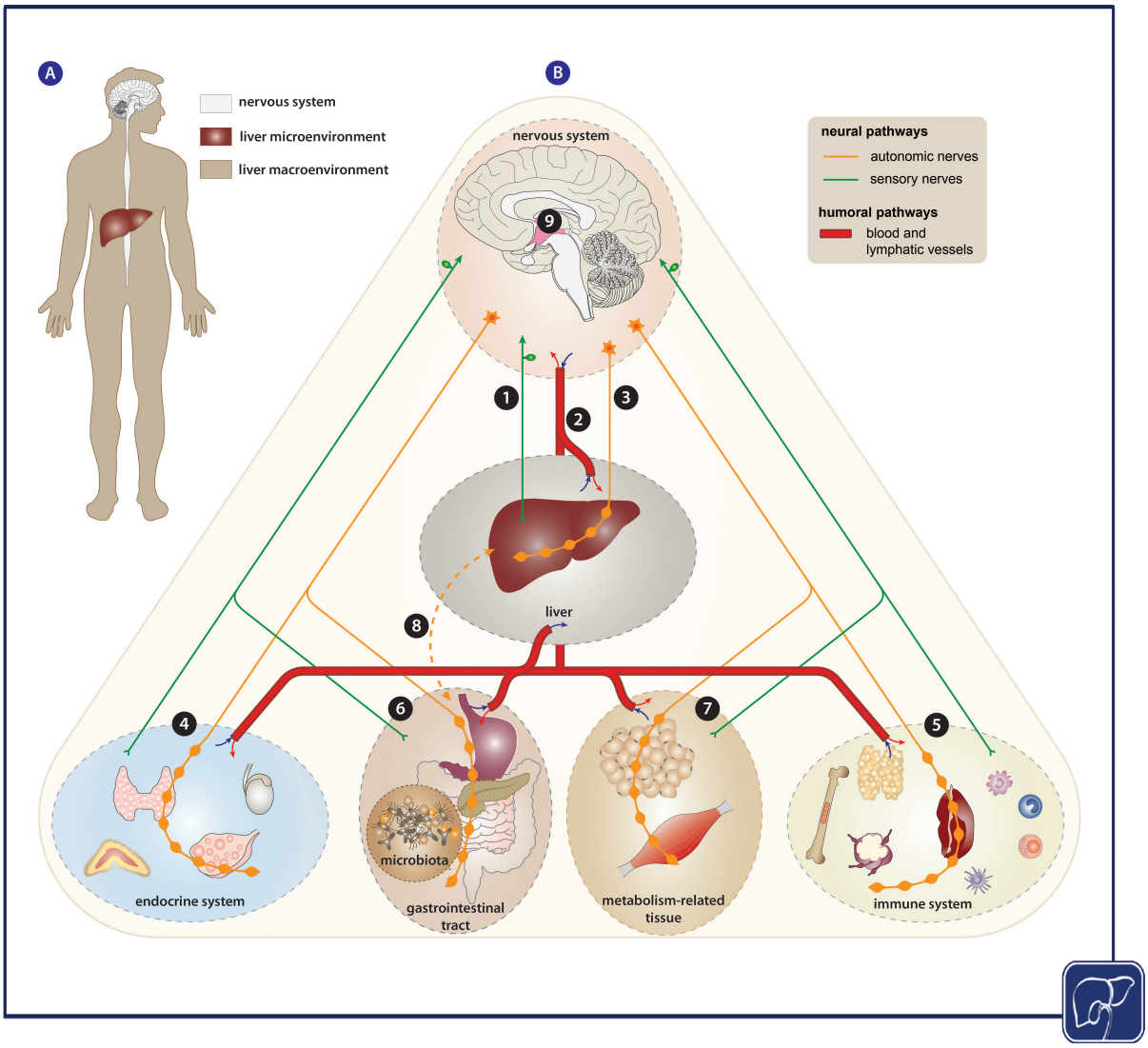

Fig. 1 Schematic illustration of the pathways mediating the influence of the nervous system on liver function. (**A**) The nervous system regulates liver function through neural and humoral pathways directly, by modulating processes in the liver microenvironment (liver tissue), and indirectly, by modulating processes in the liver macroenvironment. The liver macroenvironment includes endocrine and immune organs and cells, as well as organs of the digestive tract, skeletal muscle, adipose tissue, and other tissues and organs. (**B**) The nervous system processes signals transmitted by sensory nerves (1) and humoral pathways from the liver and other compartments of the body (2), ad based on these signals regulates hepatic function through sympathetic and parasympathetic nerves (3). In addition, the nervous system also acts on the liver indirectly, by the neuroendocrine–immune network, which is composed of bidirectional interactions between the nervous system, endocrine glands (4), and the immune system (5). Moreover, the nervous influence on the liver is also related to the activity of other organs of the digestive tract and the microbiota (6) as well as metabolism-related tissues (7). It is possible that liver functions are also influenced by interorgan interactions mediated by nerves interconnecting, for example, the liver and organs of the gastrointestinal tract via local autonomic ganglia and enteric nervous system (8). At the level of the brain, the hypothalamus is the main coordinating structure of the brain–liver axis (9).[5]

circadian changes in liver function and signals from liver participate on homeostatic feedback control of central circadian rhythms.[10]

Brain–liver interactions are mediated by signaling molecules such as neurotransmitters, neuromodulators, hormones, and cytokines. The brain–liver axis allows the brain, based on signals from the liver but also from other compartments of the body, to comprehensively regulate the activity of the liver and to respond to possible alterations in its activity. In addition, this axis mediates the influence of psychosocial factors (e.g., stressors) on the liver.[1]

The brain–liver axis plays an important role not only in physiological situations but also during pathological processes.[5] For example, the nervous system modulates liver repair and regeneration, influences processes related to inflammation, liver fibrosis as well as the origin and progression of other pathological processes occurring in the liver (hepatic steatosis, cirrhosis, hepatocellular carcinoma [HCC]).[5] The nervous system also exerts a modulatory influence on diseases that are related to liver function at the systemic level, an example is the action of the brain on processes related to diabetes and obesity.[1]

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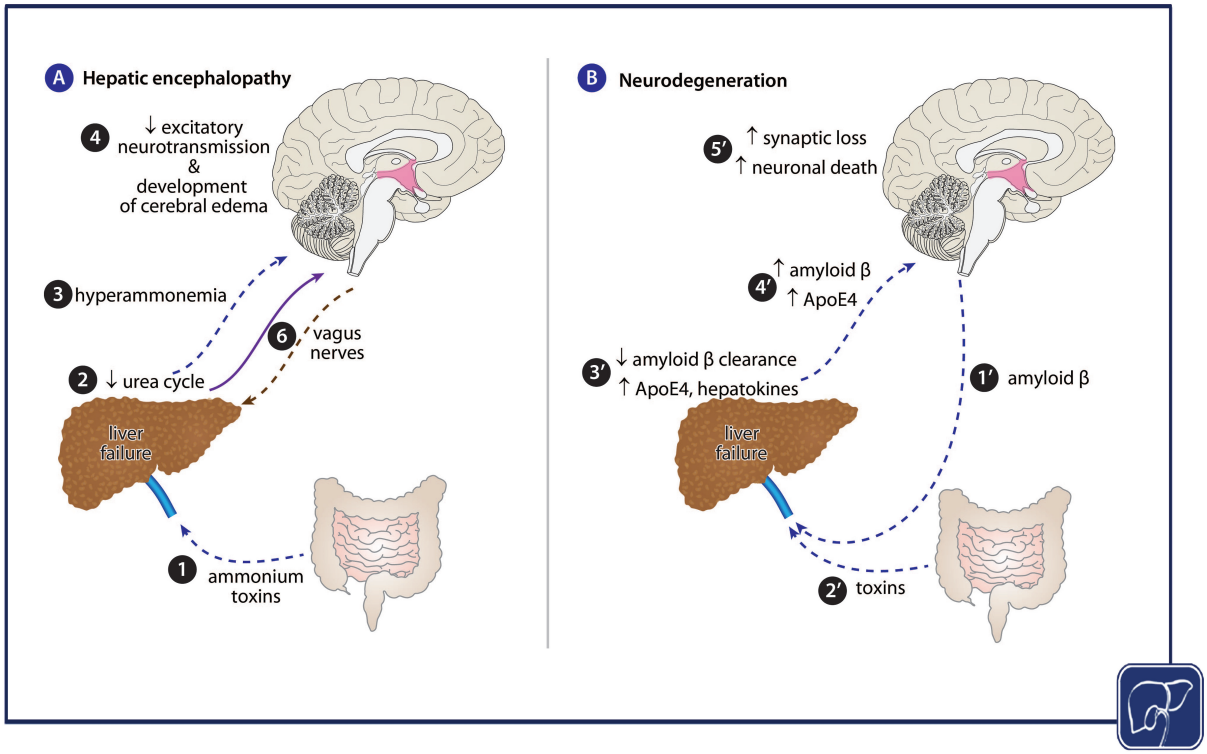
A Hepatic encephalopathy
4 ↓ excitatory neurotransmission & development of cerebral edema
3 hyperammonemia
6 vagus nerves
2 ↓ urea cycle
liver failure
1 ammonium toxins
B Neurodegeneration
5′ ↑ synaptic loss ↑ neuronal death
4′ ↑ amyloid β ↑ ApoE4
3′ ↓ amyloid β clearance ↑ ApoE4, hepatokines
1′ amyloid β
liver failure
2′ toxins

Fig. 2 Schematic illustration of the processes through which the liver–brain axis is involved in the development of hepatic encephalopathy (HE) (**A**) and promotes the development of neurodegeneration (**B**). HE develops as a result of impaired metabolic communication across the liver–brain axis. At the beginning of the pathological cascade leading to the development of HE, intestinal bacteria and mucosal enzymes digesting proteins release ammonia, which passes from the intestine to the portal circulation of the liver and is converted to urea in the liver (1). However, in the case of liver failure, ammonia is not sufficiently converted to urea (2) and hyperammonemia develops (3), leading to impaired neuronal function and the development of HE. Ammonia can lead to a decrease in excitatory neurotransmission and trigger the development of cerebral edema (4).[7] An increase in plasma levels of aromatic amino acids and manganese, which occurs as a result of liver failure, is also implicated in the development of HE. The transmission of signals through the afferent and efferent pathways of the vagus nerve (6) also plays a role in the development of HE. Hepatic failure can also affect brain function and participate on development of neurodegeneration due to decreased hepatic clearance of amyloid β, by impaired hepatic production of ApoE4 and hepatokines (3′) as well as through other substances related to liver function such as vitamins, choline, bilirubin, and bile acids as well as endotoxins (**B**).[38]

Neural Pathways

The liver is innervated by efferent (sympathetic and parasympathetic) and afferent (vagal and spinal sensory) nerves (►**Fig. 3**). These nerves enter the liver through the hilus, forming an anterior plexus around the hepatic artery and a posterior plexus around the portal vein and bile duct. While the anterior plexus is formed by nerve fibers that originate from the left portion of the celiac plexus and the right abdominal branch of the vagus nerve, the posterior plexus is formed by nerve fibers originating from the right portion of the celiac plexus. Fibers of autonomic nerves are found in each segment of the liver and are also present around the bile ducts.[1,2,11–14]

Sympathetic innervation of the liver is provided by sympathetic preganglionic neurons, located in the intermediolateral column of the spinal cord in the T7 to T12 segments. Axons of these preganglionic neurons connect to neurons in the celiac and superior mesenteric ganglia. Nerve fibers projecting from these ganglia run in the splanchnic nerves. Sympathetic nerves enter the liver along the hepatic artery, portal vein, and bile ducts and their intrahepatic branches and release norepinephrine and neuropeptide Y in liver vessels and liver tissue from varicosities of sympathetic nerve fibers.[11,15–17]

Parasympathetic innervation of the liver is provided by preganglionic neurons of the vagus nerve located in the dorsal motor nucleus of the vagus nerve. The axons of these neurons innervate neurons in the ganglia in the hepatic hilum and portal tract. These neurons, projecting the postganglionic nerve fibers, release acetylcholine in liver.[11,16–19] From the point of view of experimental research, it is important to note that while the innervation of the portal tract is the same in different animal species, the lobular innervation is variable. In humans, the autonomic nerve fibers spread into the lobule, where they run in the space of Disse in close proximity to the stellate cells and cells of the liver parenchyma. Whereas sympathetic fibers enter the tissue of the lobule, cholinergic fibers predominate in the periportal region. However, such lobular innervation has not been demonstrated in the liver of mice and rats. Therefore, it is suggested that the neural regulation of liver functions in these animals is mediated by diffusion of neurotransmitters released in portal tract that regulate sinusoidal blood flow

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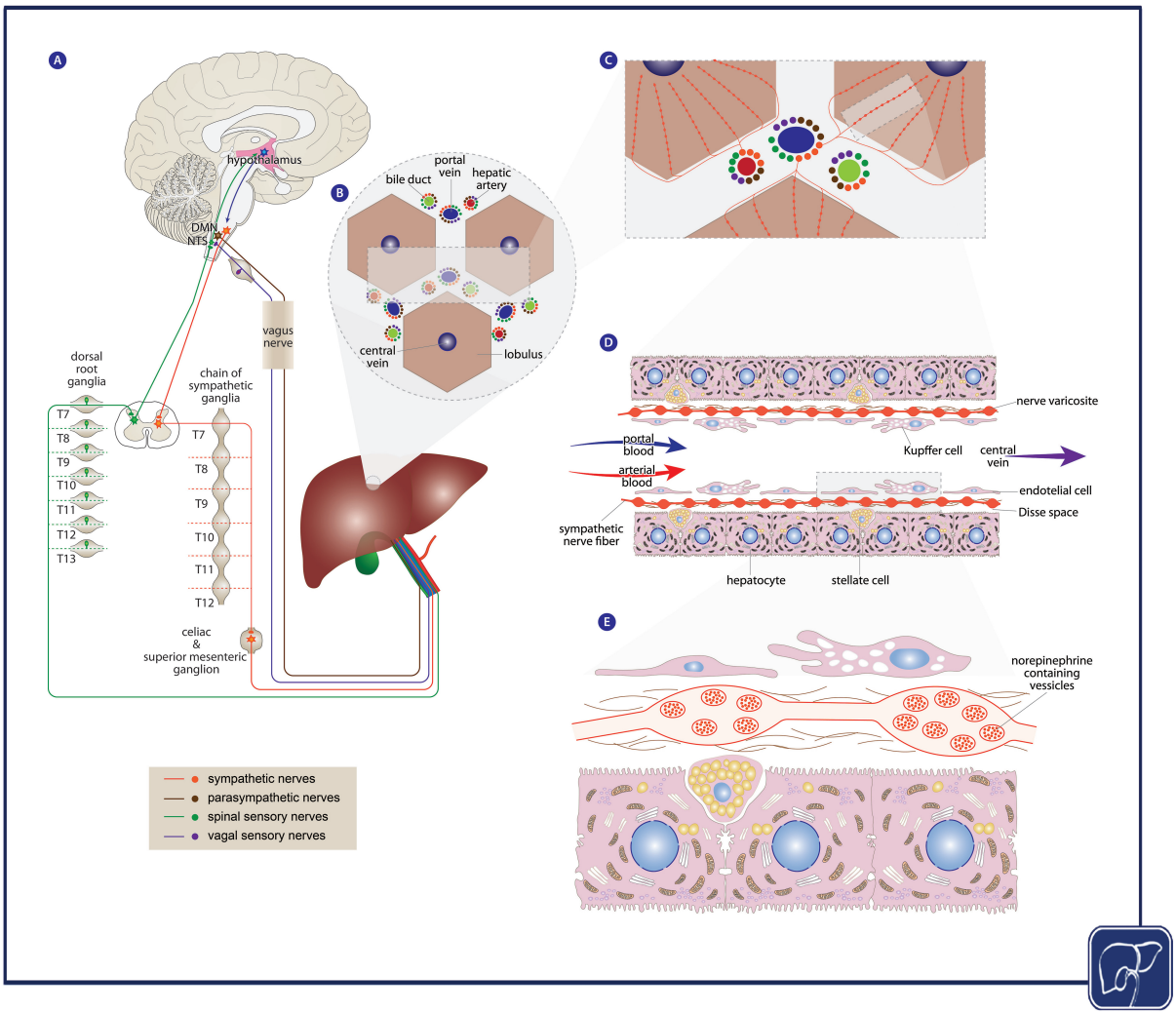

Fig. 3 Schematic illustration of liver innervation. The liver is innervated by sympathetic, parasympathetic, and sensory nerves. Sympathetic innervation is provided by preganglionic neurons whose bodies are located in intermediolateral segments T7 to T12 of the spinal cord and project their axons through sympathetic ganglia and interconnect in the celiac and superior mesenteric ganglia to postganglionic neurons that innervate the blood vessels and parenchyma of the liver. Parasympathetic innervation is provided by efferent fibers of the vagus nerve, which innervate blood vessels and bile ducts but do not penetrate significantly into the liver parenchyma. Sensory innervation is provided by spinal visceral afferent neurons whose bodies are located in the ganglia of the dorsal horns of the spinal cord (T7–T13) as well as by afferent fibers of the vagus nerve (**A**–**C**). Sympathetic nerve fibers innervating the liver parenchyma are located in the spaces of Disse, into which they release norepinephrine from the varicosities. Norepinephrine released by volume transmission acts there and influences the activity of hepatocytes, stellate cells, Kupffer cells, and endothelial cells (**D**, **E**).[22,156,157] DMN, dorsal motor nucleus of the vagus nerve; NTS, nucleus of the solitary tract.

via modulation of portal vessel tone and/or by transmission of signals across gap junctions between hepatocytes.[2,11,12,20]

The sensory innervation of the liver is provided by vagal and spinal viscerosensory neurons whose cell bodies are located in the left nodose ganglion of the vagus nerve and the T7 to T13 dorsal roots ganglia of the spinal cord. In contrast to autonomic innervation, sensory nerves do not innervate hepatocytes, and sensory innervation is thus restricted to the stroma surrounding the triads of the hepatic vasculature and bile ducts and to the extrahepatic portion of the portal vein and bile ducts.[21] The sensory nociceptive innervation of the liver does not involve its parenchyma and thus the liver, together with the brain, are two organs in which, when pathological processes are taking place, these do not induce nociception.

The sensory endings of the afferent nerves innervating the liver serve as sensors, detecting the presence and concentrations of various substances or mechanical forces. These sensory endings may include osmoreceptors, receptors detecting concentrations of ions, metabolites (glucose, lipids, amino acids), and hormones. Sensory endings containing receptors for cytokines may monitor the extent of immune responses and the presence of inflammation in liver tissue. In addition, sensory endings can also monitor hemodynamics in the liver. The sensory nerves also innervate the liver capsule, and the mechanoreceptors of these sensory nerves detect liver distension, which may increase as a result of various pathological conditions. These sensory nerves and nerves innervating the biliary tract are involved in nociception.[1,22]

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In terms of neurotransmitters, adrenergic, cholinergic, nitrergic, and peptidergic nerve fibers are involved in the innervation of the liver. In the varicosities of sympathetic and parasympathetic nerves, in addition to primary neurotransmitters, cotransmitters from the neuropeptide group are present. These neuropeptides include neuropeptide Y, vasoactive intestinal peptide, glucagon-like peptide, somatostatin, neurotensin, galanin, and serotonin. In addition to the adrenergic (sympathetic) and cholinergic (vagal) nerves, nonadrenergic/noncholinergic nerves are found in the liver, as well. These nerves synthesize nitric oxide. Neuropeptides, such as substance P and calcitonin gene-related peptides (CGRPs) are released from sensory nerve endings during activation of axon reflex.[11,12,17]

The effect of neurotransmitters on the liver depends not only on the type of neurotransmitter and the compartment where it is released, but also on the expression of the corresponding receptors by the different liver cell types. For example, hepatocytes express α- and β-adrenergic receptors,[23] cholangiocytes express α_1- and β_1-adrenergic receptors as well as M3 cholinergic receptors.[2,24,25] Hepatic stellate cells (HSCs) express α- and β-adrenergic receptors and receptors for neuropeptide Y.[26]

It should also be noted that some neurotransmitters and neuromodulators are also synthesized in liver by non-neuronal cells. An example is the synthesis of acetylcholine by immune cells. Therefore, in certain physiological and pathological situations, the activation of receptors for neurotransmitters and neuromodulators in liver tissue may not always be related to its innervation.[27]

Neuroendocrine–Immune Network

The brain may regulate liver functions also indirectly, through neuroendocrine and neuroimmune interactions (►**Fig. 1B**).[4,13] An example of neuroendocrine regulation is the action of cortisol released by the hypothalamic–pituitary–adrenocortical (HPA) axis, which influences hepatic glucose metabolism.[1] The brain influences liver functions also through other hormones such as oxytocin, vasopressin, growth hormone, and indirectly by stimulating the secretion of sex hormones by gonads. These hormones exert their effect in both physiological and pathological conditions.[28–31]

The neuroimmune effect on the liver is mediated by cortisol that exerts systemic modulatory effects on inflammation-related processes.[32] Neuroimmune regulation of liver is exerted also by the cholinergic anti-inflammatory pathway (CAP)[33–35] (for details see below). Moreover, sympathetic nerves are involved in complex neuroimmune regulation of liver functions and generally exert a stimulatory effect on inflammation either when activated by an acute stressor or an inhibitory effect when the activity of these nerves is increased repeatedly and over a long period of time.[36]

The liver itself is also part of the neuroendocrine–immune network. This organ in fact both secretes or participates in the modification of several hormones such as 25-hydroxyvitamin D, insulin-like growth factor 1, and angiotensinogen. In addition, it is significantly involved in the metabolism of certain hormones (e.g., thyroid hormones, glucagon-like peptide-1, and steroid hormones).[37] Importantly, the liver also influences brain functions through hepatokines and metabolites, such as bile acids, ammonia, bilirubin, and choline. Among the hepatokines that affect the brain are apolipoprotein E, fibroblast growth factor 21, growth differentiation factor 15, tsukushi, angiopoietin-like protein 8, liver-enriched antimicrobial peptide-2, and lipocalin-2. These substances modulate brain lipid metabolism, brain growth, food intake, maintain blood–brain barrier integrity, and may also be involved in neuroinflammation. They are also significantly involved in the development of various liver diseases as well as systemic metabolic diseases.[38]

Brain Structures, Neurotransmitters, and Neuromodulators Regulating Liver Functions

Brain structures that regulate liver function include the nuclei of the hypothalamus and brainstem (►**Table 1**). The primary integrating center of the brain–liver axis is the hypothalamus, which regulates glucose and lipid metabolism by modulating liver activity. In addition, the hypothalamic nuclei are involved in other homeostatic regulations, including regulation of plasma ions composition, plasma osmolality, and blood pressure, in addition to regulation of energy intake and expenditure. The arcuate nucleus (ARC) detects signals from the periphery informing the brain about energy status and based on these signals regulates metabolic processes in the liver. The suprachiasmatic nucleus (SCN) regulates peripheral oscillators of circadian rhythms in the liver. The paraventricular hypothalamic nucleus (PVN) represents the coordinating center that regulates sympathetic and parasympathetic output to the liver. The PVN mediates the regulatory influence of the ARC, SCN, ventromedial and dorsomedial hypothalamic nucleus, circumventricular organs, and coordinates the activity of components of the neuroendocrine stress response, such as the HPA axis and the sympathoadrenal system. It is also involved in mediating the effects of pancreatic and thyroid hormones on the liver via neural pathways and plays prominent role in regulation of glycemia (►**Fig. 4A, B**).[17,39–41]

The sensory nerves transmit signals from the liver to the neurons of the nucleus of the solitary tract (NTS). These neurons process signals from all visceral organs and tissues. Subsequently, the NTS projects to other brain structures, some of which regulate sympathetic and parasympathetic output to the liver (►**Fig. 4C**).

The dorsal motor nucleus of the vagus nerve and the lateral hypothalamus are involved in the regulation of inflammatory processes in the liver. These structures, through the efferent pathways of the vagus nerve, inhibit the infiltration and proinflammatory activity of macrophages in the liver, thereby dampening inflammatory processes in this organ.[42]

At the brain level, several neurotransmitters as well as neuropeptides are involved in the regulation of liver function. For example, thyrotropin-releasing hormone influenced the liver via brainstem structures (e.g., left dorsal vagal complex), stimulating hepatic blood flow and liver

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Table 1 Overview of selected brain structures that represent the central component of the brain–liver axis

Brain structure	Function	Role in the brain–liver axis
Brainstem		
Nucleus of the solitary tract (NTS)	Relay station for information transmitted by sensory neurons from the liver (part of the dorsal vagal complex)	Reflex responses: liver→liver liver→other organ other organ→liver
Area postrema (AP)	Sensory circumventricular organ (part of the dorsal vagal complex)	Input of humoral signals to brain circuits
Dorsal motor nucleus of the vagus nerve (DMNV)	Parasympathetic vagal output in the liver (part of the dorsal vagal complex)	Vagal regulation of liver activity
Rostral ventrolateral medulla (RVLM)	Sympathetic premotor neurons	Regulation of sympathetic outflow into the liver
Hypothalamus		
Paraventricular hypothalamic nucleus (PVN)	Coordination of the neuroendocrine–immune network	Regulation of glycemia, food intake, autonomic output into the liver
Arcuate nucleus (ARC)	Regulation of food intake, sensory circumventricular organ	Regulation of parasympathetic output in the liver, input of humoral signals to brain circuits,
Ventromedial nucleus (VMN) Dorsomedial nucleus (DMN) Lateral hypothalamus (LH)	Hypothalamic centers regulating food intake	Regulation of food intake and autonomic output into the liver
Suprachiasmatic nucleus (SCN)	Primary brain circadian pacemaker	Regulation of circadian rhythms in the liver
Subfornical orfan (SFO), Organum vasculosum laminea terminalis (OVLT)	Sensory circumventricular organ	Input of humoral signals to brain circuits

cell proliferation, and acting protectively against experimental injury via the vagus nerve pathways. Corticotropin-releasing factor injected into the cerebral ventricles inhibits hepatic blood flow and promotes the extent of experimental liver injury and this via sympathetic nerve pathways. Neuropeptide Y stimulates bile secretion via the left dorsal vagal complex. Similarly, neuropeptides such as β-endorphin and bombesin act at the level of the brain but also regulate liver cell proliferation in addition to bile secretion.[43,44]

Neural Regulation of Liver Function and Systemic Homeostasis

The autonomic nerves are involved in the regulation of liver functions and thus participate on maintenance of systemic homeostasis. In humans, sympathetic nerves also reach into the liver tissue, where they innervate the cells of the liver parenchyma. Abundant portal innervation maintains the flow of blood and bile, directly by maintaining the tone of the vascular and biliary systems and indirectly by regulating sinusoidal flow, which is an essential determinant of optimal metabolic function of the liver.[11,45,46] The endings of autonomic nerves that innervate the interlobular bile ducts, bile ducts, and Hering's ducts are both adrenergic and cholinergic make contacts near the biliary basement membrane directly with cholangiocytes. Contacts between sympathetic nerve fibers and HSCs have also been observed. The above neuroanatomical relationships suggest a neuromodulatory action on liver functions during physiological and pathological situations.[2,47]

Experimental studies have demonstrated the influence of autonomic nerves on several processes in the liver. For example, activation of sympathetic nerves innervating the liver has been shown to increase hepatic glucose release, decrease lactate uptake or increase its release, and increase urate release. This stimulation also decreased oxygen consumption, fatty acid oxidation, very-low-density lipoprotein (VLDL) synthesis, ketone body formation, amino acid turnover, xenobiotic conjugation, and bile formation. Stimulation of the parasympathetic nerves innervating the liver, in turn, increased both basal and insulin-induced glucose utilization by the liver, increased glycogen formation, and inhibited glucagon-induced glucose release from the liver.[3,5,13,39,48–50]

The afferent nerves innervating the liver are involved in maintaining systemic homeostasis. Due to the intimate relationship between the liver and the digestive tract, the liver acts as a sensor, detecting fluctuations in osmolality, glucose, and fatty acid concentrations, as well as microbial antigens. Therefore, the pathways that transmit information from the liver play a pivotal role in systemic homeostatic regulation, including the regulation of glycemia, energy balance, and plasma osmolality.[3,5,16,48,50,51] In addition,

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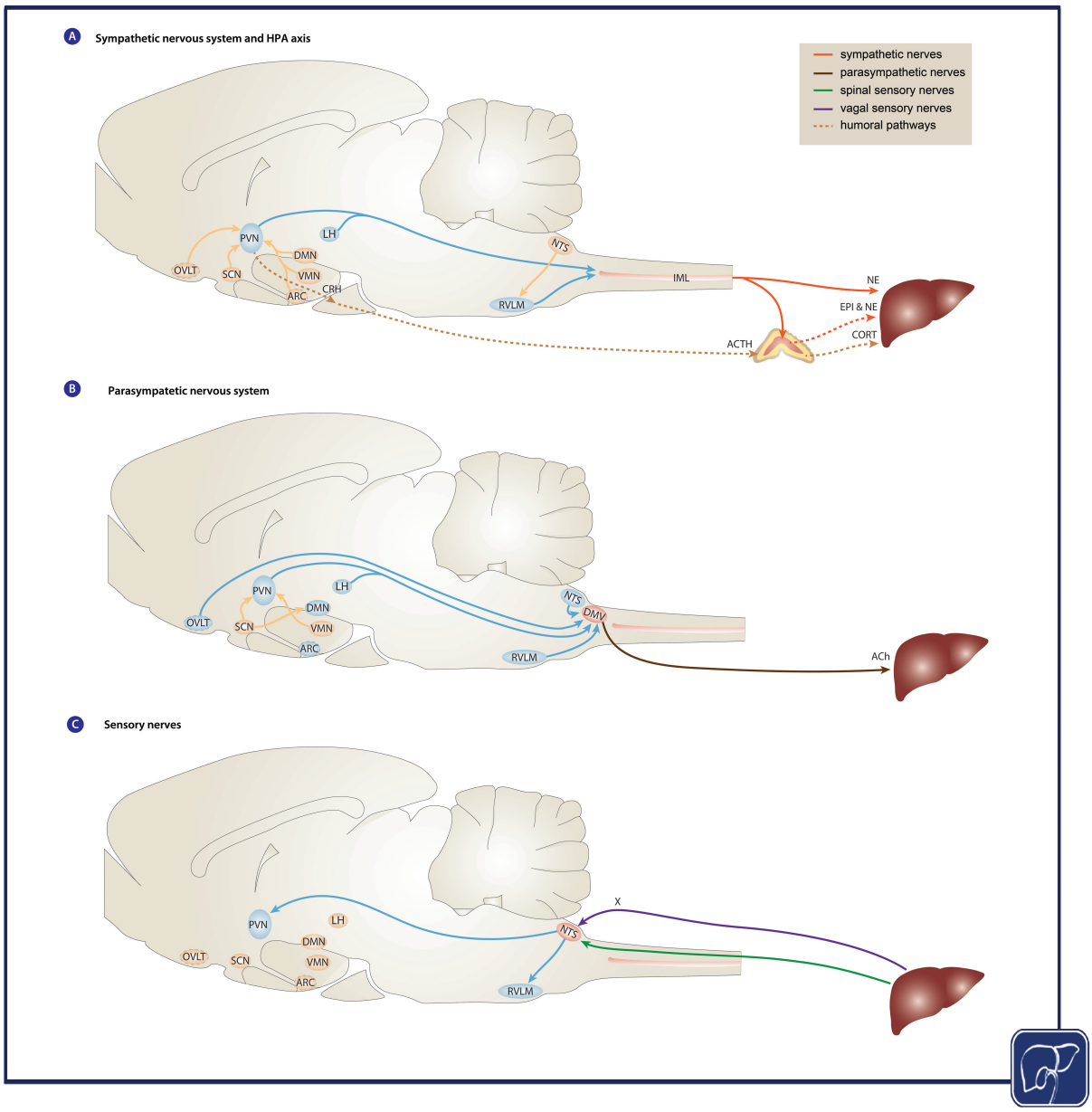

Fig. 4 Schematic illustration of brain structures that regulate sympathetic (**A**) and parasympathetic (**B**) outflow to the liver and structures that receive signals from sensory nerves (**C**) innervating the liver.[40] ACTH, adrenocorticotropic hormone; ARC, arcuate nucleus; CORT, cortisol/corticosterone; CRH, corticoliberin; DMN, dorsomedial hypothalamic nucleus; DMV, dorsal motor nucleus of the vagus nerve; EPI, epinephrine; IML, intermediolateral nucleus; LH, lateral hypothalamic area; NTS, nucleus of the solitary tract; OVLT, organum vasculosum of the lamina terminalis; SCN, suprachiasmatic nucleus; VNM, ventromedial hypothalamic nucleus.

these pathways may also be involved in protective neuroimmune responses to foreign antigens entering the portal circulation from the lumen of the digestive tract[1] (►**Fig. 5**).

A more detailed understanding of the role of neural regulation of liver function may help not only to introduce new therapeutic modalities useful in hepatology but also in the treatment of systemic metabolic abnormalities that lead to the development of obesity and diabetes.[1]

Metabolism

Glucose levels are monitored not only by the brain cells, the intestines, and carotid bodies, but also by the sensory nerves innervating the portal vein and its branches.[52–54] Nerve endings of these nerves use glucose transporter type 2 as a glucose sensor and are involved in the systemic regulation of glucose metabolism.[55] In the situation of a decrease in glucose in the portal vein, the afferent pathways of the vagus nerve are activated, which in turn activates in the brain food intake-related behavior[56,57] (►**Fig. 5A**[1–5]). In the case of an increase in glycemia, incretins such as glucagon-like peptide 1 (GLP-1) released from the small intestine as a consequence of food intake activate the afferent pathways of the vagus nerve. These afferent nerves then activate sympathetic nerves innervating the pancreas, that leads to an increase

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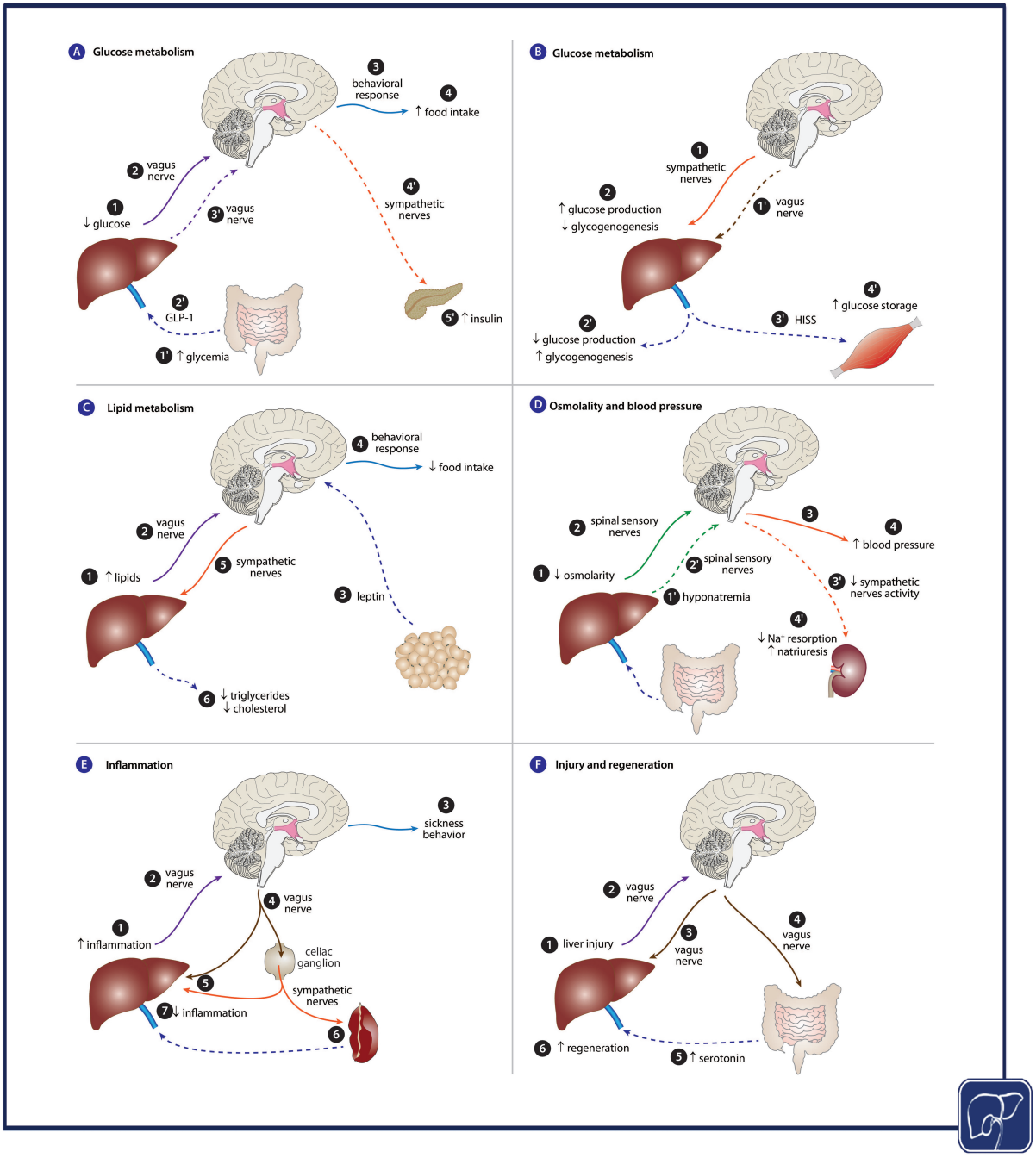

Fig. 5 Schematic illustration of homeostatic regulations in which liver innervation plays a role.[16,116] GLP-1, glucagon-like peptide-1; HISS, hepatic insulin-sensitizing substance.

in the release of insulin from the B cells[58] (►**Fig. 5A**[1'–5']). Autonomic nerves also regulate glucose metabolism directly in the liver[59,60] (►**Fig. 5B**). In support of this, Xu et al[61] demonstrated that removal of the celiac and superior mesenteric ganglia, in which sympathetic neurons innervating the liver are located, improved glucose tolerance in mice via reduction of insulin-dependent gluconeogenesis in the liver. The above findings provide evidence that sympathetic innervation in the liver exerts a stimulatory effect on gluconeogenesis. As demonstrated Liu et al[62] in mice exposed to foot shock, sympathetic nerves account for the early increase in glycemia during exposure to stress. In an experiment using cold stress, it was shown that the stress-induced rise in glycemia was mediated by activation of α_1-adrenergic receptors.[63] Conversely, activation of vagal efferent pathways suppresses glucose production in the liver and increases glycogen production[16,48,51,64] (►**Fig. 5B**). However, in contrast to these findings, Song et al[65] using chemogenetic techniques, demonstrated that activation of vagal parasympathetic neurons led to an increase in glycemia, and this was mediated by elevated hepatic gluconeogenic and lipogenic gene expression.

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The concentration of free fatty acids in the liver circulation is monitored by peroxisome proliferator-activated receptor (PPAR) gamma 2 expressed on afferent vagal fibers, which are involved in the regulation of plasma levels of lipids and other metabolites.[66] When these fibers are activated by lipids, food intake is inhibited and lipid storage is promoted[67,68] (►**Fig. 5C**). Vagal afferent pathways also mediate the relationship between hepatic PPARγ2 expression, peripheral adiposity, insulin resistance, and hypertension.[69–71] Vagal efferent pathways are involved in leptin-induced reduction of liver lipids by increasing hepatic triglyceride secretion and lowering lipogenesis.[72] Recent findings, however, point to a much more complex role for vagal innervation of the liver. Indeed, vagal sensory neurons have been found to be involved in the development of both diet-induced obesity and hepatic steatosis, as well as anxiety-like behavior. Thus, vagal innervation of the liver may represent a link between metabolic and behavioral alterations related to fatty liver disease.[73] Sympathetic nerves, stimulate triglyceride-rich VLDL secretion, for example during fasting.[39,74] Sympathetic innervation of the liver is also involved in the stimulation of ketone bodies formation and theirs release from the liver.[3,16,74]

Hepatic afferent fibers of the vagus nerve that detect substances present in the portal circulation are also activated by gastrointestinal hormones such as cholecystokinin, somatostatin, and leptin.[75–77] The transmission of signals related to the concentrations of these hormones is involved in the complex regulation of metabolism and energy intake and expenditure in the body.[1]

Bile Synthesis, Secretion, and Flow

The biliary system is densely innervated from two sources, namely via the parasympathetic fibers of the vagus nerve and the sympathetic fibers of the celiac plexus. The biliary system may also be innervated by branches of the phrenic nerve. These nerves are located in close proximity to the biliary microenvironment. Gallbladder innervating neurons that are relatively nonexcitable, are driven by vagal stimuli, and their activity is modulated by inflammatory mediators, hormones, and peptides released from sensory nerve fibers. The function of the gallbladder and biliary system is influenced also by neuromodulators, both at the brain and liver levels (e.g., substantia P, galanin, nitric oxide, vasoactive intestinal polypeptide, bombesin, thyrotropin-releasing hormone).[44,78]

Sympathetic nerves innervating the liver decrease bile acid secretion and bile flow. This inhibitory effect is mediated by α_1-adrenergic receptors[79] and probably acts at the canalicular level.[80] Conversely, the vagus nerve stimulates bile secretion.[43,81] This effect is related also to vagaly mediated increase in bicarbonate secretion into bile and depends on activation of M3 cholinergic receptors.[25,82] Interestingly, recent findings suggest that in patients with biliary atresia, increased parasympathetic innervation in biliary remnants represents a positive prognostic marker.[83] Thus, parasympathetic innervation has, in generally, a positive effect on bile production and secretion.

In the case of biliary injury, sympathetic, parasympathetic, and sensory nerves promote proliferation of cholangiocytes and limit their apoptosis. These appear to be either redundant or synergistic actions.[2]

Body Fluids Osmolality, Volume, and Arterial Blood Pressure, Blood Perfusion in the Liver

Because of its anatomical relationships to gastrointestinal tract, the liver plays an important role in regulating the osmolality and ionic composition of the blood. Spinal sensory neurons, whose cell bodies are located in the dorsal root ganglia of the spinal cord, monitor blood osmolality in the portal vein via osmoreceptors.[84] These neurons are also able to detect changes in the concentrations of certain ions (e.g., Na^+).[85,86] Thus, the brain is informed about changes in osmolality and ion concentrations before changes in systemic circulation occur.[1,86–88]

In the case of a decrease in osmolality in the portal vein due to water intake, signals transmitted through sensory neurons innervating the liver induce an increase in the activity of sympathetic nerves that regulate peripheral vascular resistance.[89,90] This mechanism is part of the so-called pressor reflex (►**Fig. 5D**[1–4]). Changes in osmolality are detected by transient receptor potential vanilloid 4 channels expressed on sensory neurons innervating the portal vein.[1,91]

In the case of detection of hypernatremia in the portal vein, afferent signaling from the liver transmitted by spinal afferent pathways to the brain induces a decrease in the activity of sympathetic nerves innervating the kidney, resulting in a decrease in resorption and an increase in Na^+ excretion by the kidney. This response is also referred to as the hepatorenal reflex[92] (►**Fig. 5D**[1'–4']). It is suggested that the reduction of the hepatorenal reflex in patients with end-stage liver cirrhosis is involved in the pathogenesis of the hepatorenal syndrome, which is characterized by hypernatremia.[1,16,87]

Autonomic nerves regulate blood flow through the liver. Activation of sympathetic nerves reduces flow through the hepatic arteries[3] and this effect is mediated by activation of α-adrenergic receptors, which induce vasoconstriction of the hepatic artery and a reduction in sinusoidal wall permeability by an effect on HSCs, resulting in a reduction in total blood flow through the liver.[93] Only recently, Dohi et al[94] have shown that norepinephrine directly induced reversible contraction of quiescent HSCs, further supporting the involvement of sympathetic nerves in the regulation of hepatic blood flow at the level of hepatic sinusoids. On the other hand, acetylcholine and vasoactive intestinal peptide released from varicosities of parasympathetic nerve fibers induce relaxation of sinusoids.[16,95]

Inflammation

Both afferent (viscerosensory) and autonomic (visceromotor) nerves are involved in the neural regulation of inflammation in the liver. These nerves are part of several homeostatic regulations that prevent excessive inflammatory response in the liver. The nervous regulation of inflammation in the liver depends on the type of nerves, the factors that triggered the inflammation in the liver, the extent of the inflammatory process, the mutual sympathovagal interactions, the type of liver cells that are affected by the neurotransmitters released

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from the autonomic nerves as well as the type of receptors that these cells express.[49,96]

The afferent vagal nerve fibers innervating the liver express receptors for cytokines (e.g., IL-1β and TNF-α), thereby participating in monitoring the concentrations of proinflammatory substances in the portal circulation and liver tissue. These vagal fibers that are part of the inflammatory reflex, transmit inflammation-related signals to the brain, specifically to the NTS (►**Fig. 5E**). NTS neurons subsequently induce activation of neurons in the dorsal motor nucleus of the vagus nerve and thus activate the efferent fibers of the vagus nerve. These fibers form the efferent arm of the inflammatory reflex, which is referred to as the CAP.[97]

CAP represents one of the fundamental regulatory mechanisms involved in both tonic inhibition of the activity of immune cells that are continuously exposed to foreign antigens (e.g., immune cells in the gut) and reflex inhibition of inflammation. CAP can induce anti-inflammatory action directly in innervated tissues via acetylcholine released from the varicosities of the vagus nerve fibers (e.g., in the intestine). In addition, vagal efferent pathways in the celiac ganglion also synapse to sympathetic postganglionic neurons whose axons form the splenic nerve. These axons of sympathetic neurons in the spleen release norepinephrine, which, by binding to adrenergic receptors on immune cells, induces the release of acetylcholine from immune cells, which in turn inhibits inflammation by binding to the α7nAChR of splenic macrophages.[97,98]

CAP also plays a role in the regulation of inflammation in the liver (►**Fig. 5E**).[99] The role of CAP in the regulation of inflammation in the liver was already pointed out in 2000, when Borovikova et al[100] demonstrated that electrical stimulation of the cervical segment of the vagus nerve directly suppressed lipopolysaccharide-induced TNF-α production in the liver. Later, it was shown that both nicotine, a nonspecific nAChRs agonist, and PNU-282987, a selective α7nAChRs agonist, suppressed hepatic inflammation induced by ischemia-reperfusion injury in the liver.[101,102]

It is suggested that CAP exert its anti-inflammatory effects in the liver via activation of α7nAChRs expressed by Kupffer cells.[103] This is supported by the observation that hepatic vagotomy exacerbated inflammation in a mouse model of nonalcoholic steatohepatitis (NASH), whereas agonists of α7nAChRs expressed by Kupffer cells suppressed hepatic inflammation in NASH by suppressing the NF-κB pathway. In addition, Fu et al[104] found in a mouse model of acute liver failure that chemical activation of CAP reduced the extent of liver injury, and this was mediated through inhibition of MAdCAM1/α4β7-related gut-derived proinflammatory lymphocyte infiltration. Recently, Song et al[105] demonstrated that α7nAChRs-mediated liver regeneration and protected the liver from chemical damage and this was through stimulation of IL-22 production.

Anti-inflammatory effect in the liver might be induced also by electrical stimulation of the vagus nerve (VNS).[106] Thus, VNS may represent a new method in the treatment of liver diseases in which inflammation plays an important. The rationale for this assumption is supported by the finding of Elkattawy et al[107] who showed that VNS exerted a significant beneficial effect on inflammatory and metabolic parameters in a rat model of nonalcoholic fatty liver disease.

In addition to the vagal efferent pathways, which act via the CAP, the inflammatory process in the liver may also be regulated by sympathetic and sensory nerves. These nerves may potentiate inflammatory processes in the liver by modulating the activity of B lymphocytes and other immune cells.[13] Proinflammatory action of sympathetic nerves in the liver is mediated by the binding of norepinephrine to α_1-adrenergic receptors on Kupffer cells.[108]

In addition to the modulatory effect of the brain on inflammation in the liver, hepatic inflammation, or other liver dysfunctions may itself influence brain functions and promote the development of neuroinflammation.[109] In patients with liver cirrhosis, peripheral inflammation is thought to be involved in the development of neuroinflammation in the brain, leading to impaired neurotransmission and thus cognitive and motor alterations.[110] The development of neuroinflammation in the brain is a consequence of impaired liver function and is related to the effects of increased plasma levels of proinflammatory cytokines and toxic metabolites, as well as the transfer of immune cells to the brain and gut microbiota to the blood.[111,112]

Liver Tissue Homeostasis and Regeneration

In addition to the regulation of liver functions, nerves are also involved in the maintenance of tissue homeostasis. Tissue homeostasis determines the types and numbers of cells, their location in the tissue, extracellular matrix characteristics, capillary density, and other tissue characteristics.[113] For example, acetylcholine appears to induce proliferation of cholangiocytes.[25,114] Similar effect is induced also by activation of α_1-adrenergic receptors by norepinephrine.[24,115]

Hepatocytes exhibit high replicative ability, which provides the liver with a considerable regenerative capacity. The autonomic innervation of the liver plays a significant role in the regulation of this regenerative capacity.[96,116] As reported by Kiba,[117,118] the neural influence on liver regeneration results from the integration of neurohumoral signals and the regulatory action of the lateral hypothalamic area and the ventromedial hypothalamic nucleus.

The importance of neural modulation of liver regeneration is demonstrated by the fact that autonomic nerves regulate several functions of HSCs, which play an important role in liver regeneration but also in pathological processes such as liver fibrosis. Sympathetic nerves activate HSCs and promote the formation of collagen fibers by these cells.[119] These nerves may also be involved in promoting fibrotic processes in the liver during pathological situations. In addition, hepatic sympathetic nerves inhibit the proliferation of HSCs, which may limit the regeneration of the injured liver.[3,16,96,115,120] As demonstrated by Zhou et al,[121] sympathetic nerves mediate the inhibitory effect of stress on liver regeneration through activation of macrophage β_2-adrenergic receptors. The intrahepatic nervous system also appears to modulate the functions of hepatic oval cells, which are thought to represent hepatic stem cells or progenitor cells.

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The role of autonomic nerves in liver regeneration demonstrated also findings that hepatic vagotomy reduced the proliferative response to partial hepatectomy, whereas sympathetic nerve activity was reduced in the early stages of the regenerative process.[122–125]

In animal experiments using a model of toxic liver injury, sympathetic nerves in the liver have been found to exert proinflammatory and profibrotic effects by acting on HSCs.[2] Similarly, profibrotic effects are exerted also by the neuropeptide CGRP released in the liver from sensory nerves. Meanwhile, this effect of CRGP on liver fibrosis is mediated by TGFβ1/Smad2 and YAP signaling pathways.[126] Conversely, parasympathetic innervation of the liver exhibited a protective, anti-inflammatory effect during its chemically induced injury. This effect was mediated by activation of α7nAChRs expressed by liver macrophages.[2,127–129]

In addition to autonomic nerves, sensory nerves also play a role in liver regeneration because these nerves are a part of the liver stem cell niche.[130] In support of this, Chen et al[131] demonstrated that genetic depletion of sensory nerves impaired liver regeneration in mice with partial hepatectomy. In addition, it was found that sensory nerves synthesizing CGRP promote hepatocyte proliferation and liver regeneration.[132,133]

Circadian Rhythms

The primary pacemaker is the SCN. This hypothalamic nucleus coordinates circadian rhythms in peripheral tissues and organs via neural and humoral pathways.[134] In the liver, these pathways regulate circadian rhythms in metabolism and detoxification.[3,16,135–137] In the case of sympathetic/parasympathetic imbalance, the transmission of signals from the SCN to the liver and thus circadian rhythmicity in liver function may be disrupted.[138] A more detailed understanding of the neural regulation of circadian rhythms in the liver may be useful, for example, in optimizing the timing and dosage of drugs in the treatment of liver diseases but also other diseases.[138]

Interorgan Neural Regulations

In addition to the influence of the central nervous system, liver functions are also modulated by interorgan nerve signaling. This is a regulatory neural mechanism that is based on the transmission of signals from one organ to another via neural and humoral pathways. This regulation involves the liver–brain–gut interactions (►**Fig. 1**) but also heart–brain–liver interactions as well as interactions between liver and other organs and tissues. These interactions allow the liver to modulate, via neural and humoral pathways, the activity of other organs as well as other organs to modulate liver functions.[139] For example, Imai et al[140] demonstrated that hepatic activation of extracellularly regulated kinase signaling induced B cell proliferation in the pancreas, and this effect was mediated via neural pathways that transmitted metabolic signals. In this case, the liver, via neural pathways, induced pancreatic B cell mass expansion to normalize glycemia.

Liver–Brain–Gut Neural Arc

This neural arc plays an important role in homeostatic regulation involving the brain and liver.[50] For example, it modulates immune homeostasis in the gastrointestinal tract. The hepatic afferent pathways of the vagus nerve are part of this neural circuit, which is involved in the indirect monitoring of the gut microenvironment and the transmission of relevant signals from portal vein to the NTS of the brainstem. This nucleus then regulates the activity of the efferent vagal pathways, which connect to the enteric nervous system. The role of liver–brain–gut arc demonstrated the fact that surgical and chemical disruption of afferent vagal fibers at the hepatic level reduced the number of colonic pT_{reg} cells.[140] In addition, this arc may be involved in the effect of hyperammonia and increased concentrations of other toxins on brain function in liver disease. These toxic substances, by entering the blood vessels of the brain, act on its cells and may underlie neurocognitive impairment. In addition, these substances activate the afferent pathways of the vagus nerve and activate the vagovagal reflex. As a result, activation of the efferent pathways of the vagus nerve modulates the activity of peripheral regulatory T cells in the gut through the action of acetylcholine on antigen-presenting cells.[6]

Heart–Brain–Liver Neural Arc

Recently, McCracken et al[141] using multiorgan imaging have demonstrated the existence of a so-called heart–brain–liver axis. The authors speculate that this axis may have a role within a context of shared multiorgan risk factors. Given the importance of neural regulation of liver and heart function and the importance of the transmission of signals from these organs through afferent neural pathways to the brain, the importance of neural communication between these three components of the heart–brain–liver axis may be considered. It is then conceivable that interventions targeting the neural connections between the components of this axis could be used in the treatment of several liver, metabolic, and cardiovascular diseases.

Psychoneuroimmunology, Stress, and the Liver

Psychoneuroimmunology investigates the mechanisms and pathways that mediate the influence of psychological processes on the functioning of the organism and the impact of processes in peripheral tissues and organs on brain functions.[142] Thus, psychoneuroimmunology studies provide, for example, an understanding of how stress affects the functioning of the organism under physiological conditions, but also what role it plays in the onset and progression of disease.[143]

The adverse effects of stress on the organism may result from inappropriate activation of neuroendocrine stress response systems, namely the sympathoadrenal system and the HPA axis (►**Fig. 6**). Indeed, intense and/or chronic stress can lead to allostatic overload of tissues and organs due to their exaggerated activation induced by stress hormones and thus may activate or potentiate pathological

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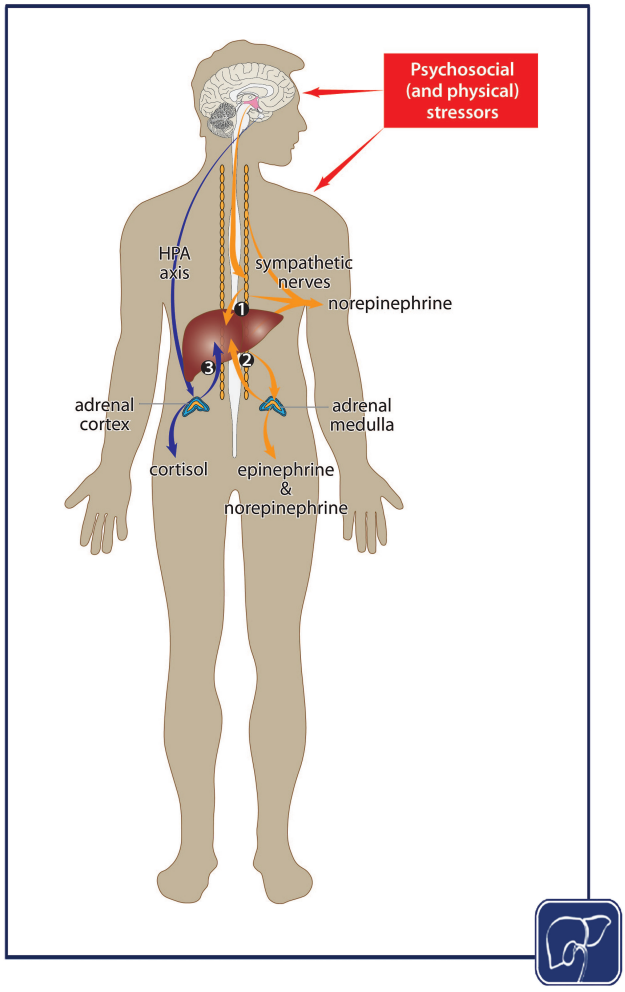

Fig. 6 Schematic illustration of the components of the neuroendocrine stress response. Stressors can affect liver function by norepinephrine released from sympathetic nerve endings (1), by epinephrine and norepinephrine released from the adrenal medulla into the systemic circulation (2), and by cortisol released into the blood from the adrenal cortex (3). Stress can also affect liver function indirectly, by modulating the liver macroenvironment as well as by behavioral stress response.[145]

processes associated with the onset and progression of diseases.[144] Admittedly, this also applies to the liver.[145–148]

Stress and the Incidence of Liver Disease

For example, the stimulatory effect of stress on the development of HCC in patients with liver cirrhosis is suggested by a meta-analysis published by He et al.[149] These authors found that nonselective β-blockers, such as nadolol and carvedilol, which block the effect of the stress mediators, epinephrine and norepinephrine, on cells, reduced the incidence of HCC in cirrhotic patients. Propranolol had a similar effect, but only in the European and American patient populations. Cho et al[150] in a cohort study involving 142,005 Korean adults demonstrated that depression was positively and independently associated with incident hepatic steatosis and hepatic steatosis plus high probability of advanced fibrosis, particularly in obese individuals. Kang et al[151] in a cross-sectional study involving 171,321 apparently healthy adults, found that higher perceived stress was independently associated with an increased prevalence of nonalcoholic fatty liver disease.

Stress and Liver Disease Progression

Stress promotes liver damage and may thus be involved in the progression of liver disease.[145] For example, Xu et al[152] found that chronic psychological stress in rats promoted liver damage and fibrosis. In doing so, this effect depended on altered gut microbiota diversity and increased intestinal permeability to lipopolysaccharide. Liu et al[153] demonstrated that an anxiety-like state in rats induced liver damage and this was mediated through the EFGR/PI3K/AKT/NF-κB pathway, which led to the production of proinflammatory factors in the liver.

Our Findings

The influence of psychosocial factors on the course of liver disease is also supported by our observations in patients with chronic hepatitis. In clinical practice in a cohort of more than 100 patients with chronic hepatitis C, we observed a significant impact of psychosocial factors both in the acquisition of hepatitis C and in the course of infection and its consequences and prognosis of patients. The most common factor, in 70% of patients, was a history of intravenous drug use; approximately 5% had acquired the infection during plasma donation before 1992. In terms of psychosocial factors, they were more likely to come vulnerable and at-risk backgrounds with a history of alcohol or other substance abuse in the immediate family environment, also living with a single parent, abroad or in a lower sociohygienic standard, growing up in marginalized communities. The patient's own attitude toward their disease played a significant role in the course and severity of the consequences of chronic hepatitis. The overwhelming majority of patients, especially those with hepatitis C, had a disorder of adaptation and behavior, the so-called neurasthenic syndrome. In our study, the 2-item Generalised Anxiety Disorder (GAD) questionnaire was used to assess neurasthenic syndrome, with patients scoring 3 or more points being considered as high-probability cases of GAD. A simple stratification tool was used to assess the severity of liver damage, less than 5 points for chronic hepatitis C, followed by the classification system based on the Child–Pugh score for liver cirrhosis (stage A: 5–6 points, stage B: 7–9 points, stage C: 10–15 points, with additional points assigned as necessary). Complications were scored using additional points allocated for the presence of portal vein thrombosis, hepatorenal syndrome, spontaneous bacterial peritonitis, variceal bleeding, and HCC. Patients who had scored 3 points or more on the GAD questionnaire 5 to 10 years prior to the detection of severe liver damage scored 10 points or more jumped from a score of less than 5 points to the most severe stage, scoring 11 points or more, with rapid progression of liver disease. On the other hand, those who

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scored less than 3 points on the GAD questionnaire remained without progression of liver disease.

We found that patients with depressive attitude, larval depression, anxiety, with the need to fight against injustice and to obtain compensation for harm to health (after iatrogenic acquisition of hepatitis during plasma donation) ultimately reached more severe degrees of liver damage after 25 to 30 years of infection, compared with those with a balanced psychological attunement, harmonious family background, and support. The very factor of the patient's "self-injury" also led to more severe liver damage resulting in cirrhosis with the need for transplantation, sometimes in coincidence with portal vein thrombosis, which was a contraindication to it. Conversely, patients with a positive attitude, appreciating the gifts of being and living, were able to survive for a significant period of 20 to 40 years without signs of cirrhosis of the liver or severe fibrosis. Euthymia and a positive attitude helped to significantly improve the prognosis despite adverse circumstances (e.g., liver cancer and inability to explant the liver when attempting transplantation), up to the 10-year survival achieved. Our observations demonstrate that the brain–liver axis plays a role not only in the physiological regulation of liver functions but also in modulating the course of liver disease (for more details see[5]).

Clinical Implications

The investigation of the pathways and mechanisms underlying the brain–liver axis not only provides a better understanding of the role of brain–liver interactions in the maintenance of homeostasis, but also allows to elucidate the importance of this axis in the etiopathogenesis of liver diseases and thus the identification of new therapeutic targets in hepatology. This research has also provided the basis for the definition of a new scientific field, the neurobiology of liver disease.

Currently, research related to neurobiology of liver disease focuses largely on describing the pathways and mechanisms involved in the onset and progression of alcohol-associated liver disease, nonalcoholic fatty liver disease, cholestatic liver disease, hepatitis, cirrhosis, and HCC. Obtained data indicate that, although there are exceptions, in general, sympathetic and sensory nerves exert a stimulatory effect on pathological processes occurring in the liver, whereas parasympathetic nerves exert an inhibitory (protective) effect. Experimental and clinical data also demonstrate that chronic stress exerts an adverse effect on liver function through the sympathetic nerves. This effect is prominent, especially in patients with liver disease. Therefore, it seems reasonable to use as an adjunctive therapy in the treatment of liver disease interventions reducing the impact of chronic stress on the patient's organism. These interventions may include psychotherapy, pharmacological blockade of adrenergic signaling (e.g., propranolol) or sympathetic denervation.[154] Other potential therapeutic interventions that are based on insights into the neurobiology of liver disease include pharmacological, electrical, or ultrasound stimulation of the CAP. Since disturbance of the sympathovagal balance can affect the prognosis of liver diseases, the determination of heart rate variability appears to be an effective biomarker useful in hepatology.[5,155]

Conclusion

Experimental and clinical studies demonstrate the importance of the nervous system in the regulation of liver function during physiological conditions. In addition to homeostatic, compensatory, and adaptive responses, the nervous system also mediates the influence of psychosocial factors (e.g., stressors) on the liver. Although many mechanisms mediating the influence of the nervous system on the physiological functioning of the liver have been described, several questions regarding the brain–liver axis remain unanswered. For example, it is not clear which neural pathways are part of the inflammatory reflex regulating immune homeostasis in liver tissue. The importance of innervation in liver ontogeny is also unknown. These are just some of the questions that only further neurobiological research on the brain–liver axis will be able to answer.

From a clinical point of view, it is important that knowledge of the mechanisms and pathways underlying the brain–liver axis allows better characterization of processes related to metabolic abnormalities, inflammation, fibrosis, or carcinogenesis in liver tissue (for more details see[2,4,5]). Meanwhile, knowledge related to the neural regulation of liver disease pathogenesis can be used in the prevention, treatment, and prognosis of liver disease.[5]

Data Availability Statement

Data sharing is not applicable to this article, as no new data were created or analyzed in this study.

Authors' Contributions

Both authors contributed equally to the conception, design, writing, and critical review of the manuscript. B.M. prepared figures.

Conflict of Interest

None declared.

References

1 Jensen KJ, Alpini G, Glaser S. Hepatic nervous system and neurobiology of the liver. Compr Physiol 2013;3(02):655–665
2 Miller BM, Oderberg IM, Goessling W. Hepatic nervous system in development, regeneration, and disease. Hepatology 2021;74 (06):3513–3522
3 Kandilis AN, Papadopoulou IP, Koskinas J, Sotiropoulos G, Tiniakos DG. Liver innervation and hepatic function: new insights. J Surg Res 2015;194(02):511–519
4 Zou J, Li J, Wang X, Tang D, Chen R. Neuroimmune modulation in liver pathophysiology. J Neuroinflammation 2024;21(01):188
5 Mravec B, Szantova M. The role of the nervous system in liver diseases. Hepatol Res 2024;54(11):970–980

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6 Zhu R, Liu L, Zhang G, Dong J, Ren Z, Li Z. The pathogenesis of gut microbiota in hepatic encephalopathy by the gut-liver-brain axis. Biosci Rep 2023;43(06):BSR20222524
7 Wijdicks EF. Hepatic encephalopathy. N Engl J Med 2016;375 (17):1660–1670
8 Giuffrè M, Moretti R. The gut-liver-brain axis: from the head to the feet. Int J Mol Sci 2023;24(21):15662
9 Sun X, Shukla M, Wang W, Li S. Unlocking gut-liver-brain axis communication metabolites: energy metabolism, immunity and barriers. NPJ Biofilms Microbiomes 2024;10(01):136
10 Woodie LN, Melink LC, Midha M, et al. Hepatic vagal afferents convey clock-dependent signals to regulate circadian food intake. Science 2024;386(6722):673–677
11 Saxena R. Got nerve? Autonomic innervation of the human liver. Virchows Arch 2020;477(03):383–384
12 McCuskey RS. Anatomy of efferent hepatic nerves. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01):821–826
13 Martinez-Sanchez N, Sweeney O, Sidarta-Oliveira D, Caron A, Stanley SA, Domingos AI. The sympathetic nervous system in the 21st century: neuroimmune interactions in metabolic homeostasis and obesity. Neuron 2022;110(21):3597–3626
14 Chen CC, Peng SJ, Chou YH, et al. Human liver afferent and efferent nerves revealed by 3-D/Airyscan super-resolution imaging. Am J Physiol Endocrinol Metab 2024;326(02):E107–E123
15 Kyösola K, Penttilä O, Ihamäki T, Varis K, Salaspuro M. Adrenergic innervation of the human liver. A fluorescence histochemical analysis of clinical liver biopsy specimens. Scand J Gastroenterol 1985;20(02):254–256
16 Mizuno K, Ueno Y. Autonomic nervous system and the liver. Hepatol Res 2017;47(02):160–165
17 Uyama N, Geerts A, Reynaert H. Neural connections between the hypothalamus and the liver. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01):808–820
18 Sutherland SD. An evaluation of cholinesterase techniques in the study of the intrinsic innervation of the liver. J Anat 1964;98(Pt 3):321–326
19 Amenta F, Cavallotti C, Ferrante F, Tonelli F. Cholinergic nerves in the human liver. Histochem J 1981;13(03):419–424
20 Reilly FD, McCuskey PA, McCuskey RS. Intrahepatic distribution of nerves in the rat. Anat Rec 1978;191(01):55–67
21 Berthoud HR. Anatomy and function of sensory hepatic nerves. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01):827–835
22 Berthoud HR, Münzberg H, Morrison CD, Neuhuber WL. Hepatic interoception in health and disease. Auton Neurosci 2024; 253:103174
23 Studer RK, Borle AB. Differences between male and female rats in the regulation of hepatic glycogenolysis. The relative role of calcium and cAMP in phosphorylase activation by catecholamines. J Biol Chem 1982;257(14):7987–7993
24 LeSage GD, Alvaro D, Glaser S, et al. Alpha-1 adrenergic receptor agonists modulate ductal secretion of BDL rats via Ca(2+)- and PKC-dependent stimulation of cAMP. Hepatology 2004;40(05): 1116–1127
25 LeSagE G, Alvaro D, Benedetti A, et al. Cholinergic system modulates growth, apoptosis, and secretion of cholangiocytes from bile duct-ligated rats. Gastroenterology 1999;117(01): 191–199
26 Sigala B, McKee C, Soeda J, et al. Sympathetic nervous system catecholamines and neuropeptide Y neurotransmitters are upregulated in human NAFLD and modulate the fibrogenic function of hepatic stellate cells. PLoS One 2013;8(09):e72928
27 Zheng C, Snow BE, Elia AJ, et al. Tumor-specific cholinergic $CD4^+$ T lymphocytes guide immunosurveillance of hepatocellular carcinoma. Nat Cancer 2023;4(10):1437–1454
28 Kasarinaite A, Sinton M, Saunders PTK, Hay DC. The influence of sex hormones in liver function and disease. Cells 2023;12(12): 1604
29 Mancinelli R, Franchitto A, Glaser S, et al. Vasopressin regulates the growth of the biliary epithelium in polycystic liver disease. Lab Invest 2016;96(11):1147–1155
30 Pennisi PA, Kopchick JJ, Thorgeirsson S, LeRoith D, Yakar S. Role of growth hormone (GH) in liver regeneration. Endocrinology 2004;145(10):4748–4755
31 Luo D, Jin B, Zhai X, et al. Oxytocin promotes hepatic regeneration in elderly mice. iScience 2021;24(02):102125
32 Sternberg EM. Neural regulation of innate immunity: a coordinated nonspecific host response to pathogens. Nat Rev Immunol 2006;6(04):318–328
33 Gallowitsch-Puerta M, Pavlov VA. Neuro-immune interactions via the cholinergic anti-inflammatory pathway. Life Sci 2007;80 (24-25):2325–2329
34 Occhinegro A, McAllen RM, McKinley MJ, Martelli D. Acute inhibition of inflammation mediated by sympathetic nerves: the inflammatory reflex. Neuroimmunomodulation 2023;30 (01):135–142
35 Hajiasgharzadeh K, Baradaran B. Cholinergic anti-inflammatory pathway and the liver. Adv Pharm Bull 2017;7(04):507–513
36 Reardon C, Murray K, Lomax AE. Neuroimmune communication in health and disease. Physiol Rev 2018;98(04):2287–2316
37 Rhyu J, Yu R. Newly discovered endocrine functions of the liver. World J Hepatol 2021;13(11):1611–1628
38 Yang X, Qiu K, Jiang Y, Huang Y, Zhang Y, Liao Y. Metabolic crosstalk between liver and brain: from diseases to mechanisms. Int J Mol Sci 2024;25(14):7621
39 Geerling JJ, Boon MR, Kooijman S, et al. Sympathetic nervous system control of triglyceride metabolism: novel concepts derived from recent studies. J Lipid Res 2014;55(02):180–189
40 Kalsbeek A, Fliers E. Hypothalamus. In: Pfaff DW, Volkow ND, Rubenstein JL, eds,. Neuroscience in the 21st Century: From Basic to Clinical. Cham: Springer International Publishing; 2022: 1813–1852
41 Desmoulins LD, Molinas AJR, Dugas CM, et al. A subset of neurons in the paraventricular nucleus of the hypothalamus directly project to liver-related premotor neurons in the ventrolateral medulla. Auton Neurosci 2025;257:103222
42 Chan KL, Poller WC, Swirski FK, Russo SJ. Central regulation of stress-evoked peripheral immune responses. Nat Rev Neurosci 2023;24(10):591–604
43 Yoneda M, Watanobe H, Terano A. Central regulation of hepatic function by neuropeptides. J Gastroenterol 2001;36(06):361–367
44 Yoneda M, Kurosawa M, Watanobe H, Shimada T, Terano A. Brain-gut axis of the liver: the role of central neuropeptides. J Gastroenterol 2002;37(Suppl 14):151–156
45 Lautt WW. Relationship between hepatic blood flow and overall metabolism: the hepatic arterial buffer response. Fed Proc 1983; 42(06):1662–1666
46 Lautt WW. The hepatic artery: subservient to hepatic metabolism or guardian of normal hepatic clearance rates of humoral substances. Gen Pharmacol 1977;8(02):73–78
47 Zanchi A, Reidy J, Feldman HJ, et al. Innervation of the proximal human biliary tree. Virchows Arch 2020;477(03):385–392
48 Püschel GP. Control of hepatocyte metabolism by sympathetic and parasympathetic hepatic nerves. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01):854–867
49 Ren W, Hua M, Cao F, Zeng W. The sympathetic-immune milieu in metabolic health and diseases: insights from pancreas, liver, intestine, and adipose tissues. Adv Sci (Weinh) 2024;11(08): e2306128
50 Matsubara Y, Kiyohara H, Teratani T, Mikami Y, Kanai T. Organ and brain crosstalk: The liver-brain axis in gastrointestinal, liver, and pancreatic diseases. Neuropharmacology 2022;205:108915
51 Lin EE, Scott-Solomon E, Kuruvilla R. Peripheral innervation in the regulation of glucose homeostasis. Trends Neurosci 2021;44 (03):189–202

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52 Hevener AL, Bergman RN, Donovan CM. Novel glucosensor for hypoglycemic detection localized to the portal vein. Diabetes 1997;46(09):1521–1525
53 Niijima A. Afferent impulse discharges from glucoreceptors in the liver of the guinea pig. Ann N Y Acad Sci 1969;157(02):690–700
54 Thorens B. Neuronal glucose sensing mechanisms and circuits in the control of insulin and glucagon secretion. Physiol Rev 2024; 104(04):1461–1486
55 Burcelin R, Dolci W, Thorens B. Glucose sensing by the hepatoportal sensor is GLUT2-dependent: in vivo analysis in GLUT2-null mice. Diabetes 2000;49(10):1643–1648
56 Niijima A. The effect of D-glucose on the firing rate of glucose-sensitive vagal afferents in the liver in comparison with the effect of 2-deoxy-D-glucose. J Auton Nerv Syst 1984;10(3-4):255–260
57 Yi CX, la Fleur SE, Fliers E, Kalsbeek A. The role of the autonomic nervous liver innervation in the control of energy metabolism. Biochim Biophys Acta 2010;1802(04):416–431
58 Balkan B, Li X. Portal GLP-1 administration in rats augments the insulin response to glucose via neuronal mechanisms. Am J Physiol Regul Integr Comp Physiol 2000;279(04):R1449–R1454
59 Pocai A, Obici S, Schwartz GJ, Rossetti L. A brain-liver circuit regulates glucose homeostasis. Cell Metab 2005;1(01):53–61
60 Zsombok A, Desmoulins LD, Derbenev AV. Sympathetic circuits regulating hepatic glucose metabolism: where we stand. Physiol Rev 2024;104(01):85–101
61 Xu S, Inoue M, Yoshimura Y, Kondoh K, Naruse K, Hiyama TY. Celiac and superior mesenteric ganglia removal improves glucose tolerance and reduces pancreas islet size. Neurosci Lett 2024;837:137919
62 Liu L, Huang Z, Zhang J, et al. Hypothalamus-sympathetic-liver axis mediates the early phase of stress-induced hyperglycemia in the male mice. Nat Commun 2024;15(01):8632
63 Morgan HJN, Delfino HBP, Schavinski AZ, et al. Hepatic noradrenergic innervation acts via CREB/CRTC2 to activate gluconeogenesis during cold. Metabolism 2024;157:155940
64 Shimazu T. Glycogen synthetase activity in liver: regulation by the autonomic nerves. Science 1967;156(3779):1256–1257
65 Song WJ, Cheon DH, Song H, et al. Activation of ChAT+ neuron in dorsal motor vagus (DMV) increases blood glucose through the regulation of hepatic gene expression in mice. Brain Res 2024; 1829:148770
66 Cox JE, Kelm GR, Meller ST, Spraggins DS, Randich A. Truncal and hepatic vagotomy reduce suppression of feeding by jejunal lipid infusions. Physiol Behav 2004;81(01):29–36
67 Randich A, Spraggins DS, Cox JE, Meller ST, Kelm GR. Jejunal or portal vein infusions of lipids increase hepatic vagal afferent activity. Neuroreport 2001;12(14):3101–3105
68 Warne JP, Foster MT, Horneman HF, et al. Afferent signalling through the common hepatic branch of the vagus inhibits voluntary lard intake and modifies plasma metabolite levels in rats. J Physiol 2007;583(Pt 2):455–467
69 Uno K, Yamada T, Ishigaki Y, et al. Hepatic peroxisome proliferator-activated receptor-γ-fat-specific protein 27 pathway contributes to obesity-related hypertension via afferent vagal signals. Eur Heart J 2012;33(10):1279–1289
70 Bernal-Mizrachi C, Xiaozhong L, Yin L, et al. An afferent vagal nerve pathway links hepatic PPARalpha activation to glucocorticoid-induced insulin resistance and hypertension. Cell Metab 2007;5(02):91–102
71 Uno K, Katagiri H, Yamada T, et al. Neuronal pathway from the liver modulates energy expenditure and systemic insulin sensitivity. Science 2006;312(5780):1656–1659
72 Hackl MT, Fürnsinn C, Schuh CM, et al. Brain leptin reduces liver lipids by increasing hepatic triglyceride secretion and lowering lipogenesis. Nat Commun 2019;10(01):2717
73 Hwang J, Lee S, Okada J, et al. Liver-innervating vagal sensory neurons are indispensable for the development of hepatic steatosis and anxiety-like behavior in diet-induced obese mice. Nat Commun 2025;16(01):991
74 Bruinstroop E, Pei L, Ackermans MT, et al. Hypothalamic neuropeptide Y (NPY) controls hepatic VLDL-triglyceride secretion in rats via the sympathetic nervous system. Diabetes 2012;61(05): 1043–1050
75 Horn CC, Friedman MI. Separation of hepatic and gastrointestinal signals from the common "hepatic" branch of the vagus. Am J Physiol Regul Integr Comp Physiol 2004;287(01):R120–R126
76 Nakabayashi H. Neural monitoring system for circulating somatostatin in the hepatoportal area. Nutrition 1997;13(03): 225–229
77 Shiraishi T, Sasaki K, Niijima A, Oomura Y. Leptin effects on feeding-related hypothalamic and peripheral neuronal activities in normal and obese rats. Nutrition 1999;15(7–8):576–579
78 Balemba OB, Salter MJ, Mawe GM. Innervation of the extrahepatic biliary tract. Anat Rec A Discov Mol Cell Evol Biol 2004;280 (01):836–847
79 Beckh K, Arnold R. Regulation of bile secretion by sympathetic nerves in perfused rat liver. Am J Physiol 1991;261(5 Pt 1): G775–G780
80 Friman S, Rådberg G, Svanvik J. Adrenergic influence on bile secretion–an experimental study in the cat. Acta Physiol Scand 1990;140(02):287–293
81 Baldwin J, Heer FW, Albo R, Peloso O, Ruby L, Silen W. Effect of vagus nerve stimulation on hepatic secretion of bile in human subject. Am J Surg 1966;111(01):66–69
82 Alvaro D, Alpini G, Jezequel AM, et al. Role and mechanisms of action of acetylcholine in the regulation of rat cholangiocyte secretory functions. J Clin Invest 1997;100(06):1349–1362
83 Yang J, Chen X, Wang W, et al. Role of cholinergic innervation in biliary remnants of patients with biliary atresia. Front Pediatr 2024;11:1278978
84 Niijima A. Afferent discharges from osmoreceptors in the liver of the guinea pig. Science 1969;166(3912):1519–1520
85 Lechner SG, Markworth S, Poole K, et al. The molecular and cellular identity of peripheral osmoreceptors. Neuron 2011;69 (02):332–344
86 Morita H, Ohyama H, Hagiike M, et al. Effects of portal infusion of hypertonic solution on jejunal electrolyte transport in anesthetized dogs. Am J Physiol 1990;259(6 Pt 2):R1289–R1294
87 Morita H, Abe C. Negative feedforward control of body fluid homeostasis by hepatorenal reflex. Hypertens Res 2011;34(08): 895–905
88 Ichiki T, Wang T, Kennedy A, et al. Sensory representation and detection mechanisms of gut osmolality change. Nature 2022; 602(7897):468–474
89 Tank J, Schroeder C, Stoffels M, et al. Pressor effect of water drinking in tetraplegic patients may be a spinal reflex. Hypertension 2003;41(06):1234–1239
90 May M, Gueler F, Barg-Hock H, et al. Liver afferents contribute to water drinking-induced sympathetic activation in human subjects: a clinical trial. PLoS One 2011;6(10):e25898
91 Mai TH, Garland EM, Diedrich A, Robertson D. Hepatic and renal mechanisms underlying the osmopressor response. Auton Neurosci 2017;203:58–66
92 Morita H, Matsuda T, Furuya F, Khanchowdhury MR, Hosomi H. Hepatorenal reflex plays an important role in natriuresis after high-NaCl food intake in conscious dogs. Circ Res 1993;72(03): 552–559
93 Bennett TD, MacAnespie CL, Rothe CF. Active hepatic capacitance responses to neural and humoral stimuli in dogs. Am J Physiol 1982;242(06):H1000–H1009
94 Dohi N, Yamaguchi M, Iwami K, Kaneko YK, Saito SY, Ishikawa T. Mouse liver blood flow is regulated by hepatic stellate cells in response to the sympathetic neurotransmitter norepinephrine. Life Sci 2024;359:123214

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95 Ueno T, Bioulac-Sage P, Balabaud C, Rosenbaum J. Innervation of the sinusoidal wall: regulation of the sinusoidal diameter. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01):868–873

96 Yang K, Huang Z, Wang S, et al. The hepatic nerves regulated inflammatory effect in the process of liver injury: is nerve the key treating target for liver inflammation? Inflammation 2023; 46(05):1602–1611

97 Alen NV. The cholinergic anti-inflammatory pathway in humans: state-of-the-art review and future directions. Neurosci Biobehav Rev 2022;136:104622

98 Pavlov VA, Tracey KJ. The cholinergic anti-inflammatory pathway. Brain Behav Immun 2005;19(06):493–499

99 Metz CN, Pavlov VA. Vagus nerve cholinergic circuitry to the liver and the gastrointestinal tract in the neuroimmune communicatome. Am J Physiol Gastrointest Liver Physiol 2018;315(05): G651–G658

100 Borovikova LV, Ivanova S, Zhang M, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 2000;405(6785):458–462

101 Park J, Kang JW, Lee SM. Activation of the cholinergic anti-inflammatory pathway by nicotine attenuates hepatic ischemia/reperfusion injury via heme oxygenase-1 induction. Eur J Pharmacol 2013;707(1-3):61–70

102 Li F, Chen Z, Pan Q, et al. The protective effect of PNU-282987, a selective α7 nicotinic acetylcholine receptor agonist, on the hepatic ischemia-reperfusion injury is associated with the inhibition of high-mobility group box 1 protein expression and nuclear factor κB activation in mice. Shock 2013;39(02): 197–203

103 Martínez-Meza S, Singh B, Nixon DF, Dopkins N, Gangcuangco LMA. The brain-liver cholinergic anti-inflammatory pathway and viral infections. Bioelectron Med 2023;9(01):29

104 Fu S, Ni T, Zhang M, et al. Cholinergic anti-inflammatory pathway attenuates acute liver failure through inhibiting MAdCAM1/α4β7-mediated gut-derived proinflammatory lymphocytes accumulation. Cell Mol Gastroenterol Hepatol 2024;17(02): 199–217

105 Song Z, Wu J, Jiang T, He R, Wen H. The protective effect of the vagus nerve-α7nAChR-IL-22 pathway on acute liver injury. Cytokine 2025;186:156840

106 Nishio T, Taura K, Iwaisako K, et al. Hepatic vagus nerve regulates Kupffer cell activation via α7 nicotinic acetylcholine receptor in nonalcoholic steatohepatitis. J Gastroenterol 2017;52(08): 965–976

107 Elkattawy HA, Mahmoud SM, Hassan AE, et al. Vagal stimulation ameliorates non-alcoholic fatty liver disease in rats. Biomedicines 2023;11(12):3255

108 Huan HB, Wen XD, Chen XJ, et al. Corrigendum to "Sympathetic nervous system promotes hepatocarcinogenesis by modulating inflammation through activation of alpha1-adrenergic receptors of Kupffer cells" [Brain Behav Immun 2017;59:118–134]. Brain Behav Immun 2022;104:222–225

109 D'Mello C, Swain MG. Liver-brain inflammation axis. Am J Physiol Gastrointest Liver Physiol 2011;301(05):G749–G761

110 Cabrera-Pastor A, Llansola M, Montoliu C, et al. Peripheral inflammation induces neuroinflammation that alters neurotransmission and cognitive and motor function in hepatic encephalopathy: underlying mechanisms and therapeutic implications. Acta Physiol (Oxf) 2019;226(02):e13270

111 Chen Z, Ruan J, Li D, et al. The role of intestinal bacteria and gut-brain axis in hepatic encephalopathy. Front Cell Infect Microbiol 2021;10:595759

112 D'Mello C, Swain MG. Liver-brain interactions in inflammatory liver diseases: implications for fatigue and mood disorders. Brain Behav Immun 2014;35:9–20

113 Chovatiya R, Medzhitov R. Stress, inflammation, and defense of homeostasis. Mol Cell 2014;54(02):281–288

114 Cassiman D, Libbrecht L, Sinelli N, Desmet V, Denef C, Roskams T. The vagal nerve stimulates activation of the hepatic progenitor cell compartment via muscarinic acetylcholine receptor type 3. Am J Pathol 2002;161(02):521–530

115 Francis H, LeSage G, DeMorrow S, et al. The alpha2-adrenergic receptor agonist UK 14,304 inhibits secretin-stimulated ductal secretion by downregulation of the cAMP system in bile duct-ligated rats. Am J Physiol Cell Physiol 2007;293(04):C1252–C1262

116 Kamimura K, Inoue R, Nagoya T, et al. Autonomic nervous system network and liver regeneration. World J Gastroenterol 2018;24 (15):1616–1621

117 Kiba T. The role of the autonomic nervous system in liver regeneration and apoptosis–recent developments. Digestion 2002;66(02):79–88

118 Kiba T, Tanaka K, Numata K, Saito S, Sekihara H. Hepatocyte proliferation in rats after ventromedial hypothalamic lesions: immunoreactivity patterns of proliferating cell nuclear antigen (PCNA). J Gastroenterol 1998;33(04):523–528

119 Oben JA, Roskams T, Yang S, et al. Hepatic fibrogenesis requires sympathetic neurotransmitters. Gut 2004;53(03):438–445

120 Fausto N, Campbell JS. The role of hepatocytes and oval cells in liver regeneration and repopulation. Mech Dev 2003;120(01): 117–130

121 Zhou Y, Lin X, Jiao Y, et al. A brain-to-liver signal mediates the inhibition of liver regeneration under chronic stress in mice. Nat Commun 2024;15(01):10361

122 Tanaka K, Ohkawa S, Nishino T, Niijima A, Inoue S. Role of the hepatic branch of the vagus nerve in liver regeneration in rats. Am J Physiol 1987;253(4 Pt 1):G439–G444

123 Ohtake M, Sakaguchi T, Yoshida K, Muto T. Hepatic branch vagotomy can suppress liver regeneration in partially hepatectomized rats. HPB Surg 1993;6(04):277–286

124 Iwai M, Shimazu T. Alteration in sympathetic nerve activity during liver regeneration in rats after partial hepatectomy. J Auton Nerv Syst 1992;41(03):209–214

125 Kato H, Shimazu T. Effect of autonomic denervation on DNA synthesis during liver regeneration after partial hepatectomy. Eur J Biochem 1983;134(03):473–478

126 Wang Y, Stoess C, Holzmann G, et al. Signalling of the neuropeptide calcitonin gene-related peptide (CGRP) through RAMP1 promotes liver fibrosis via TGFβ1/Smad2 and YAP pathways. Exp Cell Res 2024;442(01):114193

127 Hiramoto T, Chida Y, Sonoda J, Yoshihara K, Sudo N, Kubo C. The hepatic vagus nerve attenuates Fas-induced apoptosis in the mouse liver via alpha7 nicotinic acetylcholine receptor. Gastroenterology 2008;134(07):2122–2131

128 Li Y, Xu Z, Yu Y, et al. The vagus nerve attenuates fulminant hepatitis by activating the Src kinase in Kuppfer cells. Scand J Immunol 2014;79(02):105–112

129 Steinebrunner N, Mogler C, Vittas S, et al. Pharmacologic cholinesterase inhibition improves survival in acetaminophen-induced acute liver failure in the mouse. BMC Gastroenterol 2014; 14:148

130 Picoli CC, Costa AC, Rocha BGS, et al. Sensory nerves in the spotlight of the stem cell niche. Stem Cells Transl Med 2021;10 (03):346–356

131 Chen H, Hu B, Lv X, et al. Prostaglandin E2 mediates sensory nerve regulation of bone homeostasis. Nat Commun 2019;10 (01):181

132 Laschinger M, Wang Y, Holzmann G, et al. The CGRP receptor component RAMP1 links sensory innervation with YAP activity in the regenerating liver. FASEB J 2020;34(06):8125–8138

133 Mizutani T, Yokoyama Y, Kokuryo T, Kawai K, Miyake T, Nagino M. Calcitonin gene-related peptide regulates the early phase of liver regeneration. J Surg Res 2013;183(01):138–145

134 Shibata S. Neural regulation of the hepatic circadian rhythm. Anat Rec A Discov Mol Cell Evol Biol 2004;280(01):901–909

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135 Cailotto C, La Fleur SE, Van Heijningen C, et al. The suprachiasmatic nucleus controls the daily variation of plasma glucose via the autonomic output to the liver: are the clock genes involved? Eur J Neurosci 2005;22(10):2531–2540
136 Cailotto C, van Heijningen C, van der Vliet J, et al. Daily rhythms in metabolic liver enzymes and plasma glucose require a balance in the autonomic output to the liver. Endocrinology 2008;149(04): 1914–1925
137 Tong X, Yin L. Circadian rhythms in liver physiology and liver diseases. Compr Physiol 2013;3(02):917–940
138 Costa R, Mangini C, Domenie ED, Zarantonello L, Montagnese S. Circadian rhythms and the liver. Liver Int 2023;43(03):534–545
139 Katagiri H. Inter-organ communication involved in metabolic regulation at the whole-body level. Inflamm Regen 2023;43 (01):60
140 Imai J, Katagiri H, Yamada T, et al. Regulation of pancreatic beta cell mass by neuronal signals from the liver. Science 2008;322 (5905):1250–1254
141 McCracken C, Raisi-Estabragh Z, Veldsman M, et al. Multi-organ imaging demonstrates the heart-brain-liver axis in UK Biobank participants. Nat Commun 2022;13(01):7839
142 Ader R. On the development of psychoneuroimmunology. Eur J Pharmacol 2000;405(1-3):167–176
143 Straub RH, Cutolo M. Psychoneuroimmunology-developments in stress research. Wien Med Wochenschr 2018;168(3–4):76–84
144 McEwen BS. Protection and damage from acute and chronic stress: allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. Ann N Y Acad Sci 2004; 1032:1–7
145 Joung JY, Cho JH, Kim YH, Choi SH, Son CG. A literature review for the mechanisms of stress-induced liver injury. Brain Behav 2019;9(03):e01235
146 Chida Y, Sudo N, Kubo C. Does stress exacerbate liver diseases? J Gastroenterol Hepatol 2006;21(1 Pt 2):202–208
147 Vere CC, Streba CT, Streba LM, Ionescu AG, Sima F. Psychosocial stress and liver disease status. World J Gastroenterol 2009;15 (24):2980–2986
148 Zhang S, Ma C, Wang X, et al. Impact of Chronic Psychological Stress on Nonalcoholic Fatty Liver Disease. Semantic Scholars; 2019
149 He X, Zhao Z, Jiang X, Sun Y. Non-selective beta-blockers and the incidence of hepatocellular carcinoma in patients with cirrhosis: a meta-analysis. Front Pharmacol 2023;14:1216059
150 Cho IY, Chang Y, Sung E, et al. Depression and increased risk of non-alcoholic fatty liver disease in individuals with obesity. Epidemiol Psychiatr Sci 2021;30:e23
151 Kang D, Zhao D, Ryu S, et al. Perceived stress and non-alcoholic fatty liver disease in apparently healthy men and women. Sci Rep 2020;10(01):38
152 Xu MY, Guo CC, Li MY, et al. Brain-gut-liver axis: chronic psychological stress promotes liver injury and fibrosis via gut in rats. Front Cell Infect Microbiol 2022;12:1040749
153 Liu B, Zhang S, Sun L, et al. Unravelling the link between psychological distress and liver disease: insights from an anxiety-like rat model and metabolomics analysis. Int J Mol Sci 2023; 24(17):13356
154 Dimitriadis K, Iliakis P, Vakka A, et al. Effects of sympathetic denervation in metabolism regulation: a novel approach for the treatment of MASLD? Cardiol Rev 2025
155 Cotero V, Graf J, Miwa H, et al. Stimulation of the hepatoportal nerve plexus with focused ultrasound restores glucose homoeostasis in diabetic mice, rats and swine. Nat Biomed Eng 2022;6 (06):683–705
156 Iwai M, Kojima T, Suriawinata AA. Anatomy and function. In: Hashimoto E, ed,. Diagnosis of Liver Disease. 2nd ed. Singapore: Springer; 2019:1–18
157 Ross MH, Pawlina W. Histology: A Text and Atlas, with Correlated Cell and Molecular Biology, 6th ed. Lippincott; 2011

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